Reporter-based isolation of induced pluripotent stem cell- and embryonic stem cell-derived cardiac progenitors reveals limited gene expression variance.

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Public Summary:
Induced pluripotent stem (iPS) cells can differentiate into multiple cell types, including heart cells, and have tremendous potential for drug discovery and regenerative therapies. However, it is unknown how much variability exists between differentiated lineages from independent iPS cell lines and, specifically, how similar iPS-cell derived heart cells (iPS-CM) are to embryonic stem (ES) cell-derived heart cells (ES-CM). We generated mouse iPS cells in which expression of NKX2-5, an early cardiac transcription factor, is marked by transgenic green fluorescent protein (GFP). Isolation of iPS- and ES-derived NKX2.5-GFP+ cardiac progenitor pools, marked by identical reporters, revealed unexpectedly high similarity in genome-wide mRNA expression levels. Furthermore, the variability between cardiac progenitors derived from independent iPS lines was minimal. The NKX2-5-GFP+ iPS cells formed cardiomyocytes by numerous induction protocols and could survive upon transplantation into the infarcted mouse heart without formation of teratomas. Despite the line-to-line variability of gene expression in the undifferentiated state of ES and iPS cells, the variance narrows significantly in lineage-specific iPS-derived cardiac progenitors, and these progenitor cells can be isolated and used for transplantation without generation of unwanted cell types.

Scientific Abstract:
RATIONALE: Induced pluripotent stem (iPS) cells can differentiate into multiple cell types, including cardiomyocytes and have tremendous potential for drug discovery and regenerative therapies. However, it is unknown how much variability exists between differentiated lineages from independent iPS cell lines and, specifically, how similar iPS cell-derived cardiomyocytes (iPS-CMs) are to embryonic stem (ES) cell-derived cardiomyocytes (ES-CMs). OBJECTIVE: We investigated how much variability exists between differentiated lineages from independent iPS cell lines and how similar iPS-CMs are to ES-CMs. METHODS AND RESULTS: We generated mouse iPS cells in which expression of NKX2-5, an early cardiac transcription factor, was marked by transgenic green fluorescent protein (GFP). Isolation of iPS- and ES-derived NKX2-5-GFP(+) cardiac progenitor pools, marked by identical reporters, revealed unexpectedly high similarity in genome-wide mRNA expression levels. Furthermore, the variability between cardiac progenitors derived from independent iPS lines was minimal. The NKX2-5-GFP(+) iPS cells formed cardiomyocytes by numerous induction protocols and could survive upon transplantation into the infarcted mouse heart without formation of teratomas. CONCLUSIONS: Despite the line-to-line variability of gene expression in the undifferentiated state of ES and iPS cells, the variance narrows significantly in lineage-specific iPS-derived cardiac progenitors, and these progenitor cells can be isolated and used for transplantation without generation of unwanted cell types.

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